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<table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>(21) International Application Number: PCT/CA96/00380</p> <p>(22) International Filing Date: 7 June 1996 (07.06.96)</p> <p>(30) Priority Data: 08/475,313 7 June 1995 (07.06.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 475,313 (CIP) Filed on 7 June 1995 (07.06.95)</p> <p>(71) Applicant (for all designated States except US): THE UNIVERSITY OF SASKATCHEWAN [CA/CA]; 105 Administration Place, Saskatoon, Saskatchewan S7N 5A2 (CA).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DIMMOCK, Jonathan, Richard [CA/CA]; 78 Harvard Crescent, Saskatoon, Saskatchewan S7H 3R1 (CA). PUTHUCODE, Ramanan, Narayan [IN/CA]; #203-105 Cumberland Avenue, Saskatoon, Saskatchewan S7N 1L7 (CA).</p> <p>(74) Agents: GALE, Edwin, J. et al.; Kirby, Eades, Gale, Baker, Station D, Box 3432, Ottawa, Ontario K1P 6N9 (CA).</p> </td> <td style="width: 50%; vertical-align: top;"> <p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/CA96/00380</p> <p>(22) International Filing Date: 7 June 1996 (07.06.96)</p> <p>(30) Priority Data: 08/475,313 7 June 1995 (07.06.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 475,313 (CIP) Filed on 7 June 1995 (07.06.95)</p> <p>(71) Applicant (for all designated States except US): THE UNIVERSITY OF SASKATCHEWAN [CA/CA]; 105 Administration Place, Saskatoon, Saskatchewan S7N 5A2 (CA).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): DIMMOCK, Jonathan, Richard [CA/CA]; 78 Harvard Crescent, Saskatoon, Saskatchewan S7H 3R1 (CA). PUTHUCODE, Ramanan, Narayan [IN/CA]; #203-105 Cumberland Avenue, Saskatoon, Saskatchewan S7N 1L7 (CA).</p> <p>(74) Agents: GALE, Edwin, J. et al.; Kirby, Eades, Gale, Baker, Station D, Box 3432, Ottawa, Ontario K1P 6N9 (CA).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: SEMICARBAZONES HAVING CNS ACTIVITY AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME</p> <p>(57) Abstract</p> <p>A compound of general formula (I) useful as an anticonvulsant for disorders of the central nervous system wherein: R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen or halogen atom, or a C₁-alkyl, C₃-cycloalkyl, cyano, C₁-alkoxy or C₆₋₁₀-aryloxy group; R⁵ represents a hydrogen atom or a C₁-alkyl, C₃-cycloalkyl or C₆₋₁₀-aryl group; and X is oxygen or sulfur; or a pharmaceutically-acceptable salt thereof. The compound may be administered orally for treating convulsions in humans or animals.</p>				
<div style="display: flex; justify-content: space-between; align-items: center;"> <div> $\begin{array}{c} R^1 \\ \\ \text{---} \text{C}_6\text{H}_3 \text{---} \\ \\ R^2 \end{array} \text{---} X \text{---} \begin{array}{c} R^3 \\ \\ \text{---} \text{C}_6\text{H}_3 \text{---} \\ \\ R^4 \end{array} \text{---} \text{C} \begin{array}{l} \text{---} R^5 \\ \text{= N-N-C-NH}_2 \\ \text{H} \quad \text{O} \end{array}$ </div> <div>(I)</div> </div>				

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SEMICARBAZONES HAVING CNS ACTIVITY
AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

TECHNICAL FIELD

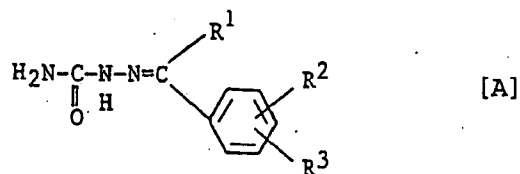
This invention relates to semicarbazone compounds having central nervous system (CNS) activity and to pharmaceutical preparations containing such compounds.

5 More particularly, the invention relates to semicarbazones having anticonvulsant properties and to the use of such semicarbazones for the treatment or prevention of convulsions and seizures in humans and animals.

10 BACKGROUND ART

There has been a great deal of interest for many years in the identification of drugs that exhibit central nervous system activity in humans and animals and that are, in particular, anticonvulsants used for
15 the treatment or prevention of epileptic seizures and other central nervous system disorders.

A previous study carried out by one of the inventors of the present invention (Dimmock et al., J. Med. Chem., 1993, 36, pp. 2243-2252) revealed that a
20 number of aryl semicarbazones of the general formula A



possess anticonvulsant activity in the maximal electroshock (MES) screen and the subcutaneous pentylenetetrazole (scPTZ) screen when administered by
25 the intraperitoneal route to mice. These screens are test systems developed to detect compounds which will afford protection to generalized tonic-clonic seizures and generalized absence convulsions, respectively. The

MES screen and the scPTZ screen have been discussed by Krall, et al. in "Antiepileptic drug development:II. Anticonvulsant drug screening", *Epilepsia*, 1978, 19, pp. 409-428; the disclosure of which is incorporated
 5 herein by reference.

Nevertheless, the compounds of formula A displayed neurotoxicity when administered by this route and the protection indices (PI, namely the ratio TD_{50}/ED_{50}) of ten representative compounds were low.

10 There is accordingly a need for compounds showing much improved anticonvulsive effects with reduced toxicity.

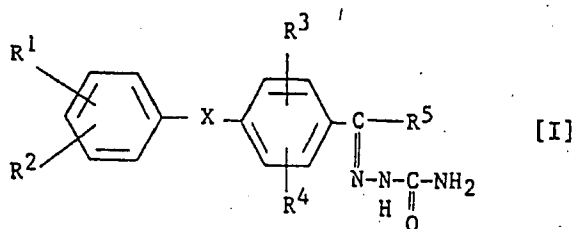
DISCLOSURE OF THE INVENTION

An object of the invention is to provide compounds
 15 having central nervous system activity.

Another object of the invention is to provide pharmaceutical compositions that have good anti-convulsive activity and acceptable neurotoxicity.

Yet another object of the invention is to provide
 20 methods of treating convulsions in humans and animal patients without producing unacceptable side effects.

According to one aspect of the invention, there is provided a compound of the general formula I



25 wherein: R¹, R², R³ and R⁴ may be the same or different and each represents a hydrogen or halogen atom, or a C₁₋₉alkyl, C₅₋₉cycloaliphatic, cyano, C₁₋₉alkoxy or C₆₋₁₀aryloxy group; R⁵ represents a hydrogen atom or a C₁₋₉alkyl, C₃₋₉cycloalkyl or C₆₋₁₀aryl group; and X is
 30 oxygen or sulfur. In the compounds of the invention,

the alkyl substituents, when present, may be straight-chained or branched.

It should be noted, however, that the compound of Formula I above in which R^1 , R^2 , R^3 , R^4 and R^5 are all hydrogen is known from Tomita et. al., "Synthesis of Aldehyde Derivatives Containing a Diphenyl Ether Nucleus", J.Pharm.Soc.Japan, 1955, 75, 1021-1023, but this reference does not disclose the anticonvulsive property of the compound.

10 According to another aspect of the invention, there is provided a composition comprising a compound of general formula I and a pharmaceutically acceptable diluent, excipient or carrier.

15 According to yet another aspect of the invention, there is provided a method of treating diseases of the central nervous system of a human or animal patient, which comprises administering to said patient an effective amount of a compound of general formula I.

20 The compounds of the invention may be administered orally and may exhibit very high potencies against CNS convulsions, e.g. they may possess ED_{50} figures (for the maximal electroshock screen in rats) in the 1-5 mg/kg range (more usually the 2-3 mg/kg range) while exhibiting an absence of neurotoxicity at the maximum
25 dose utilized (e.g. 500 mg/kg), thus leading to extremely favourable protection index (PI) values.

The compounds of the invention appear to act by one or more mechanisms which are different from those of conventional anticonvulsant drugs. Moreover, the
30 compounds of the invention may be free from some of the disadvantages of conventional anticonvulsant drugs since proconvulsant properties and effects on the activities of certain hepatic enzymes are absent in at least some of the compounds of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

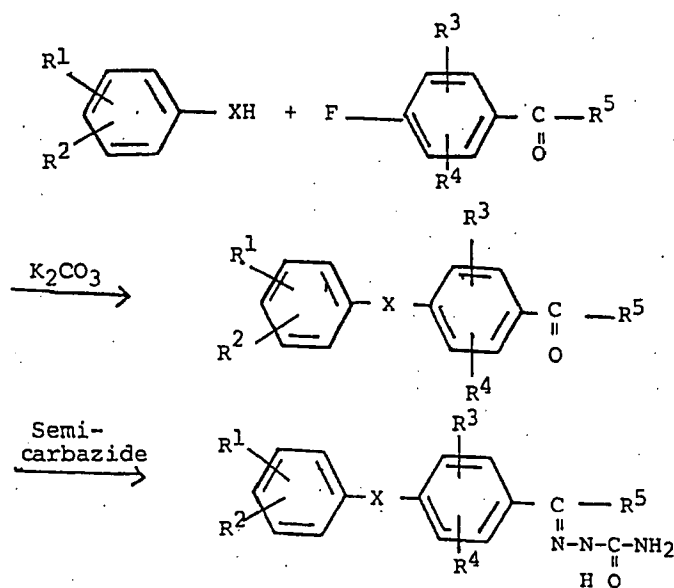
Figure 1 is a simplified representation of the postulated receptor site showing different binding regions for the compounds according to the present invention;

Figure 2 shows basic skeletal structures to indicate the compounds listed in Tables 1 to 3; and

Figure 3 shows basic chemical structures to indicate the compounds listed in Tables 4 to 6.

10 BEST MODES FOR CARRYING OUT THE INVENTIONMETHODS OF SYNTHESIS

The compounds of the present invention and compounds having related structures can be synthesized by various chemical routes, e.g. by a modification of a method disclosed by Yeager et al. ("A Convenient Method for the Preparation of 4-Aryloxyphenols", Synthesis, 1991, pp. 63-68; the disclosure of which is incorporated herein by reference). Yeager et al. describes a process for producing aryloxybenzaldehydes or aryloxyaryl ketones. These intermediates may then be reacted with semicarbazides. This route is illustrated by the reaction scheme below:



The reaction scheme shown above requires the formation of intermediate aryloxy- or arylthio-benzaldehydes or ketones by reacting appropriate phenols or thiophenols with fluorobenzaldehyde or fluoroaryl ketones in a suitable solvent (e.g. dimethylacetamide) in the presence of anhydrous potassium carbonate at temperatures in the range of 100 to 200°C under atmospheric pressure of a non-oxidizing gas (e.g. nitrogen) with reflux for a period of about 5-10 hours. After cooling and water addition, the intermediate compound may be extracted with an organic solvent (e.g. chloroform) and dried. The intermediate aryloxy(thio)benzaldehydes aryloxy(thio)aryl ketones are then converted into the desired semicarbazones by reaction with semicarbazide in an aqueous ethanolic solution for a period of one to several hours at ambient temperature, and the resulting precipitate of the final product is then collected and recrystallized. The starting materials, which are generally reacted in approximately stoichiometrical amounts, are themselves commercially available products and can, in particular, be obtained from the Aldrich Chemical Company, Milwaukee, USA.

STRUCTURES

Without wishing the invention to be limited to a particular theory, it is believed that the compounds of the present invention exert their anticonvulsive activity by aligning their molecules at a postulated receptor site in the human or animal brain, and it is theorized that such interactions take place at three areas of the receptor, namely an aryl binding site, a hydrogen bonding area and a distal binding site as illustrated in Fig. 1.

These sites are believed to react with the proximal aryl ring (the ring next to the semicarbazono group), the semicarbazono ($\text{H}_2\text{NCONHN=}$) group itself and the distal

aryl ring of the compounds, respectively. The presence of the distal aryl ring and certain substituent groups on the distal and, to a lesser extent, the proximal aryl ring in the compounds of the invention appear to
5 strengthen the attachment of the molecule at the receptor and thus increase the potency of the compounds.

A systematic synthesis and evaluation of compounds of Formula I and compounds with closely related structures has revealed the following general principles

10 (i) The substitution of the methine hydrogen attached to the carbimino carbon atom by larger groups does not significantly affect the anticonvulsive activity of the compounds; (ii) positioning of the arlyoxy or arylthio group in the ortho or meta positions
15 of the proximal ring leads to a lowering or abolition of anticonvulsive activity; (iii) the substitution of the ether oxygen by sulfur or sulfonyloxy groups leads to compounds with similar anticonvulsive activities, while other spacers lower the anticonvulsive potencies; (iv) a
20 decrease in size of the substituents on the distal aryl ring, increases anticonvulsive activity; and (v) the anticonvulsive activity is high when at least one of the substituents on the distal alkyl group is in the para position.

25 Hence, compounds of the present invention which are particularly preferred are those in which R^1 and R^2 are hydrogen or halogen (most preferably fluorine), R^3 , R^4 are each hydrogen and R^5 is hydrogen or C_{1-3} alkyl, and X is O or S (and most preferably O).

30 Particularly preferred compounds according to the present invention are 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and 4-(thiophenoxy)benzaldehyde semicarbazone. These compounds exhibit high activity in the MES screen, low toxicity and afford protection in
35 the corneal kindled rat screen without negative features, such as proconvulsant properties.

Incidentally, the kindled rat screen is described by R.J. Racine in "Modification of Seizure Activity by Electrical Stimulation. II. Motor Seizure", Electroencephalogr.Clin.Neurophysiol., 1972, 32, 281-294, and by G. Skeen et al. In "Development of Kindled Seizures Following Electrical Stimulation via the Cornea", Soc.Neurosci., 1990, 16(1), 307; the disclosures of which are incorporated herein by reference.

10 PHYSIOLOGICAL ACTIVITY

The compounds of the present invention may in some cases have quite high neurotoxicity when injected intraperitoneally in mice. For example, neurotoxicity was found to be present in approximately 65% of the compounds tested and quantitation of the bioactivities of the compounds of the invention has revealed PI's in the range of 2-14 in the MES screen and 1-3 in the scPTZ screen. However, it has been found that such neurotoxicity disappears or is reduced to an acceptable level when the compounds are administered orally to rats. Moreover, while the compounds exhibit high activity in both the MES screen and the scPTZ screen when administered intra-peritoneally, the activity in the MES screen remains high when the compounds are administered orally, but the activity in the scPTZ screen may decline. For example, for the compound 4-(4'-fluorophenoxy)benzaldehyde semicarbazone, oral dosing of rats produced an ED₅₀ figure in the rat oral screen of 1.59 mg/kg and a PI of greater than 315. However, the compound did not afford protection in the scPTZ screen at a dose of 125 mg/kg and only 10% of the rats were protected at a dose of 250 mg/kg. An absence of neurotoxicity at the maximum dose utilized (500 mg/kg) led to exceptionally high protection indices.

ADMINISTRATION

The compounds of the invention may be administered orally to humans, preferably at dosages of 50-75 mg/kg, generally in the form of compositions with inert pharmaceutically-acceptable compounds, for example diluents (e.g. calcium phosphate dihydrate, calcium sulfate dihydrate, cellulose, dextrose, lactose, mannitol, starch, sorbitol, sucrose and sucrose-based materials), binders and adhesives (e.g. acacia, cellulose derivatives, gelatin, glucose, polyvinylpyrrolidone (PVP), alginates, sorbitol, pregelatinized starch or starch paste and tragacanth), disintegrants (e.g. alginates, cellulose and cellulose derivatives, clays, cross-linked PVP, starch and starch derivatives), lubricants (e.g. polyethylene glycols, stearic acids, salts and derivatives, surfactants, talc and waxes), glidants (cornstarch, silica derivatives and talc), and colors, flavors and sweeteners (e.g. FD&C and D&C dyes and lakes, flavor oils and spray-dried flavors, artificial sweeteners and natural sweeteners).

The compositions may be prepared in any one of the conventional forms for oral administration, e.g. powders, capsules, tablets, caplets, lozenges, solutions, syrups, etc.

The invention is described in more detail in the following Examples, which are nevertheless not intended to limit the scope of the invention.

EXAMPLE 1

The compounds 2a to 5v shown in Table 1 below were synthesized by the method previously mentioned. The structures of the listed compounds correspond to those shown in Fig. 2 identified by the same first number (2, 3, 4 or 5), with only the substituents being identified in Table 1.

Table 1. Aryl Substituents, Physical Data and Anticonvulsant Evaluation after Intraperitoneal Injection into Mice and Oral Administration to Rats of the Compounds in Series 2-5

				intraperitoneal injection in mice ^a					oral administration to rats ^b						
compound	aryl substituents	m.p.(°C)	yield %	MES screen		scPTZ screen		toxicity screen		MES screen					
				0.5h	4h	0.5h	4h	0.5h	4h	dose (mg/kg)	0.25h	0.5h	1h	2h	4h
<u>2a</u>	H	198-199	40	--	--	--	--	--	--	50	--	--	2	1	1
<u>2b</u>	4-F	210-212	48	--	--	--	--	--	--	30	0	0	1	2	4
<u>3</u>	H	224-225	70	--	300	--	--	--	--	50	--	--	--	--	--
<u>4a</u>	H	224-225	60	100	300	--	--	--	--	50	--	--	3	4	4
<u>4b</u>	4-F	233-234	65	30	100	--	--	--	--	50	2	4	4	4	4
<u>4c</u>	4-Cl	225-226	40	30	30	30	--	300	30	50	4	4	4	4	4
<u>4d</u>	4-Br	225-226	60	30	30	--	--	300	30	50	1	4	4	4	4
<u>4e</u>	4-I	221-222	71	30	30	100	300	300	100	50	3	4	4	4	4
<u>4f</u>	4-CH ₃	219-221	50	30	100	--	--	--	--	50	3	4	4	4	4
<u>4g</u>	4-C ₆ H ₅	280	72	--	300	--	300	--	300	12.5	--	--	--	3	1

compound	aryl substituents	m.p.(°C)	yield %	intraperitoneal injection in mice ^a						oral administration to rats ^b						
				MES screen		scPTZ screen		toxicity screen		MES screen						
				0.5h	4h	0.5h	4h	0.5h	4h	dose (mg/kg)	0.25h	0.5h	1h	2h	4h	
<u>4h</u>	4-OCH ₃	218-220	60	100	100	--	--	--	300	50	--	4	4	4	4	4
<u>4i</u>	4-OC ₆ H ₅	209-210	55	--	300	--	--	--	--	50	--	--	--	1	1	1
<u>4j</u>	4-CN	218-220	40	30	30	30	30	300	100	12.5	2	4	4	4	4	4
<u>5a</u>	2-F	228-230	42	100	300	300	--	--	--	50	2	4	4	4	4	4
<u>5b</u>	3-F	209	42	30	300	100	--	300	300	50	4	4	4	4	4	4
<u>5c</u>	2,3-F ₂	225	50	100	100	300	--	--	--	12.5	--	3	4	4	4	4
<u>5d</u>	2,4-F ₂	229-230	42	30	30	100	--	--	--	50	3	4	4	4	4	4
<u>5e</u>	2,5-F ₂	230	65	100	300	100	--	300	300	12.5	--	1	1	4	4	1
<u>5f</u>	2,6-F ₂	232	30	30	30	300	300	300	300	12.5	0	2	4	4	4	4
<u>5g</u>	3,4-F ₂	212-213	86	100	30	30	300	--	--	50	2	4	4	4	4	4
<u>5h</u>	2-Cl	207-208	42	30	30	100	300	300	--	50	3	4	4	4	4	4

compound	aryl substituents	m.p.(°C)	yield %	intraperitoneal injection in mice ^a					oral administration to rats ^b				
				MES screen		scPTZ screen		toxicity screen		MES screen			
				0.5h	4h	0.5h	4h	0.5h	4h	0.25h	0.5h	1h	2h
				0.5h	4h	0.5h	4h	0.5h	4h	dose (mg/kg)	0.25h	0.5h	1h
<u>5i</u>	3-Cl	185-186	35	30	100	30	300	300	100	50	--	4	4
<u>5j</u>	3,4-Cl ₂	216-217	45	300	30	--	--	--	300	50	--	2	4
<u>5k</u>	2-F,4-Cl	225-226	60	30	30	--	--	100	30	12.5	2	4	4
<u>5l</u>	2-Cl,4-F	209-210	59	30	30	--	--	100	300	50	4	4	4
<u>5m</u>	2-Br,4-F	203-205	40	100	100	300	--	300	300	50	4	4	4
<u>5n</u>	2-CH ₃	205	25	30	100	100	100	300	300	12.5	--	4	4
<u>5o</u>	3-CH ₃	205-206	35	30	100	--	--	100	300	12.5	--	4	3
<u>5p</u>	4-C ₂ H ₅	210	40	30	30	300	--	300	100	12.5	--	2	4
<u>5q</u>	4-n-C ₃ H ₇	215	53	100	100	300	--	--	300	12.5	--	1	2
<u>5r</u>	4-s-C ₄ H ₉	192-193	38	100	30	--	100	300	100	12.5	--	2	3
<u>5s</u>	4-t-C ₄ H ₉	200-202	48	100	30	--	100	100	100	12.5	--	--	4

compound	aryl substituents	m.p.(°C)	yield %	intraperitoneal injection in mice ^a				oral administration to rats ^b				
				MES screen	scPTZ screen	toxicity screen	dose (mg/kg)	MES screen				
				0.5h	4h	0.5h		0.5h	1h	2h	4h	
<u>5t</u>	4-t-C ₈ H ₁₇	190	30	--	--	--	300	-	-	-	-	-
<u>5u</u>	4-O-n-C ₄ H ₉	203	35	300	100	300	300	12.5	--	--	--	2
<u>5v</u>	4-O-n-C ₇ H ₁₅	204-206	20	--	--	300	-	-	-	-	-	-
	Phenytoin			30	30	--	100	100	-	-	-	-
	Carbamazepine			30	100	100	300	300	-	-	-	-
	Valproic acid			--	--	300	--	--	-	-	-	-

^a Doses of 30, 100 and 300 mg/kg were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 h and 4 h after injections were made.

The lines -- indicate an absence of anticonvulsant activity and neurotoxicity.

^b The figures in the screen indicate the number of rats out of 4 which were protected. The lines -- mean that no activity was demonstrated and the designation - indicates that the compound was not screened.

The details of the syntheses of the various compounds are indicated below.

SYNTHESIS OF INTERMEDIATES

The 3-phenoxybenzaldehyde used as a starting material required in the synthesis of compound 3 was obtained from the Aldrich Chemical Company, Milwaukee, WI. The intermediate aryloxyaryl and arylthioaryl aldehydes required in the synthesis of the other compounds were prepared as follows.

Anhydrous potassium carbonate (0.12M) was added to a solution of the appropriate phenol or thiophenol (0.15M) and 4-fluorobenzaldehyde, 4-fluoroacetophenone or 4-fluoropropiophenone (0.14M) in dimethylacetamide (100mL). The mixture was heated under reflux at 155°C under nitrogen and the progress was monitored by thin layer chromatography (TLC) using a solvent system of benzene:methanol (9:1 by volume). After approximately 5-10 hours, the mixture was cooled and water (100mL) was added. The reaction mixture was extracted with chloroform (2x100mL) and the combined organic extracts were washed with aqueous sodium hydroxide solution (4% w/v) and water. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo and the resultant oil was distilled under reduced pressure to give the appropriate aryloxyaryl, arylthioaryl aldehyde or ketone. The purity of the distillate was checked by thin layer chromatography (TLC) using benzene:methanol (9:1 by volume) as the solvent. The ¹H NMR spectrum of a representative intermediate, namely 4-phenoxybenzaldehyde, was as follows: δ (CDCl₃): 9.94 (s, 1H, CHO), 7.82-7.88 (2t, 2H, ortho H of proximal aryl ring), 7.38-7.46 (3t, 2H, meta H of proximal aryl ring), 7.20-7.27 (3t, 1H, para H of distal aryl ring), 7.03-7.12 (3t, 4H, ortho and meta H of distal aryl ring).

SYNTHESIS OF FINAL COMPOUNDS

A mixture of semicarbazide hydrochloride (0.01M), sodium acetate (0.01M) and water (10mL) was added slowly to a stirring solution of the aryloxyaryl or
5 arylthioaryl aldehyde (0.01M) in ethanol (95%, 30mL). The reaction mixture was stirred at room temperature for 1-2 hours, the precipitate was collected, washed with ether, dried and recrystallized from 95% ethanol (compounds 3, 4b, 4e, 4h, 5b-3, 5k-e, 5v), absolute
10 ethanol (compounds 4a, 4c, 4d, 4g, 4i, 5a, 5f-j, 5u) or methanol (compound 4f). The literature melting point (°C) of compound 4a was 219-220°C.

The melting points indicated for the various compounds are uncorrected. Elemental analyses (C,H,N)
15 are were within 0.4% of the calculated values except for compound 5n (calcd. for $C_{15}H_{15}N_3O_2$:N,15.60. Found: N, 14.80). 1H NMR spectroscopy was undertaken using a BRUKER AM 300 FT (trademark) NMR instrument. Thin layer chromatography (TLC) was performed using silica gel
20 sheets with a fluorescent indicator.

SYNTHESIS OF COMPOUNDS OF TYPE 15 OF FIGURE 3

3-Benzyloxybenzaldehyde required in the synthesis of the unsubstituted compound was obtained from the Aldrich Chemical Company, Milwaukee, WI. The other
25 intermediate aldehydes were prepared as follows.

Benzoyl chloride or 4-chlorobenzoyl chloride (0.05M) was added to a solution of 4-hydroxybenzaldehyde (0.04M) in pyridine (100mL). After standing overnight at room temperature, the reaction mixture was poured
30 onto acetic acid (2N, 100mL). The precipitate was collected, washed with water and recrystallized from water-methanol to give 4-benzoyloxybenzaldehyde and 4-(4-chlorobenzoyloxy)benzaldehyde required in the synthesis of 68 and 69 respectively. 4-Phenylsulfonyl-
35 benzaldehyde used in the synthesis of 70 was prepared as follows. A mixture of sodium benzenesulfinate (0.11M)

and 4-fluorobenzaldehyde (0.1M) in dry dimethylsulfoxide (75mL) was stirred at 100°C for 18h under nitrogen and then poured onto ice (~200g). The precipitate was collected, washed with water and recrystallized from ethanol (95% v/v). Finally, benzenesulfonyl chloride or 4-methylbenzenesulfonyl chloride (0.20M) was added dropwise to a stirred solution of 4-hydroxybenzaldehyde (0.16M) in dichloromethane (90mL) and triethylamine (3-5mL) at 0 to 10°C over a period of 10 min. After a further 15 min., the reaction mixture was diluted with dichloromethane and successively extracted with water, hydrochloric acid (10% w/v), saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying the organic extract, the solvent was removed affording the intermediate products required for further syntheses. The compounds were homogenous by TLC using a solvent system of benzene:methanol (7:3) and the melting points were in accord with literature values.

These intermediate aldehydes were reacted with semicarbazide as described previously.

SYNTHESIS OF COMPOUNDS OF TYPES 17 AND 18 OF FIGURE 3

These compounds were prepared from the appropriate aryloxyaryl and arylthioaryl aldehydes using literature methodologies (Dimmock, J.R.; McColl, J.M.; Wonko, S.L.; Thayer, R.S.; Hancock, D.S. Evaluation of the thiosemicarbazones of some aryl alkyl ketones and related compounds for anticonvulsant activities. Eur. J. Med. Chem. 1991, 26, 529-534; and Dimmock, J.R.; Puthucode, R.N.; Lo, M.S.; Quail, J.W.; Yang, J.; Stables, J.P. Structural modifications of the primary amino group of anticonvulsant aryl semicarbazones. Pharmazie, 1996, 51, 83-88.). The time of heating the reactants under reflux was six hours, while the times of stirring the reactants at room temperature were eight, ten and fourteen hours. In one case, the reaction

mixture was heated at 60°C for 0.5 hours. All compounds of this type were recrystallized from ethanol (95% v/v).

DETERMINATION OF LOG P VALUES

The log P figures were determined by a previously reported procedure (Dimmock, J.R.; Phillips, O.A.; Wonko, S.L.; Hickie, R.A.; Tuer, R.G.; Ambrose, S.J.; Reid, R.S.; Mutus, B.; Talpas, C.J. Evaluation of some Mannich bases of conjugated styryl ketones and related compounds versus the WiDr colon cancer in vitro. Eur. J. Med. Chem. 1989, 24, 217-226.) except that solutions were made using 1-octanol to which buffer was added. The λ_{\max} and ϵ values of the compounds were obtained in 1-octanol and not phosphate buffered saline, pH 7.4 due to the low aqueous solubilities of the compounds.

EXAMPLE 2

An initial anticonvulsant evaluation of the compounds prepared according to Example 1 was undertaken by administering the compounds by the intraperitoneal route to mice. Protection and/or neurotoxicity was noted 0.5 and 4 hours after administering doses of 30, 100 and 300 mg/kg of each semicarbazone to the animals. These results are presented in Table 1 above.

All of the compounds were active in the MES screen except compounds 2a,b,5t,v and protection was afforded by 60% of the compounds in the scPTZ test. Neurotoxicity was displayed by approximately 70% of the semicarbazones. Bioactivity was quantitated for selected compounds and these data are given in Table 2 below:

Table 2. Evaluation of Selected Compounds in the MES, scPTZ and Neurotoxicity Screens after Intraperitoneal Injection in Mice

MES screen				scPTZ screen				neurotoxicity screen				PI
Compound	t	ED ₅₀ (mg/kg)	slope	t	ED ₅₀ (mg/kg)	slope	t	TD ₅₀ (mg/kg)	slope	$\left(\frac{TD_{50}}{ED_{50}}\right)_{MES}$	$\left(\frac{TD_{50}}{ED_{50}}\right)_{scPTZ}$	
		(h)	(95% CI)		(SE)	(h)		(95% CI)	(SE)			
<u>4b</u>	1	12.86 (10.54-17.09)	8.28 (3.00)	1	>54	--	1	108.03 (71.52-157.52)	3.69 (0.96)	8.40	--	
<u>4f</u>	1	14.65 (10.44-19.23)	5.59 (1.91)	1	88.55 (45.52-173.94)	1.87 (0.57)	2	203.73 (132.44-271.13)	4.29 (1.31)	13.91	2.30	
<u>5a</u>	0.5	20.69 (18.68-22.14)	18.59 (5.63)	0.5	>220	--	2	170.01 (146.81-191.65)	12.36 (3.80)	8.22	--	
<u>5c</u>	1	45.78 (41.39-52.15)	15.53 (5.71)	1	>350	--	2	292.55 (209.59-379.29)	5.78 (1.77)	6.39	--	
<u>5d</u>	0.25	11.25 (6.68-19.16)	2.78 (0.86)	0.25	57.85 (30.13-93.95)	1.70 (0.54)	1	96.81 (77.60-113.81)	11.50 (4.08)	8.61	1.67	
<u>5g</u>	1	14.48 (9.53-18.91)	4.62 (1.35)	0.5	72.78 (49.01-99.12)	4.27 (1.34)	2	94.80 (59.86-156.29)	3.17 (1.09)	6.55	1.30	
<u>5i</u>	0.5	27.69 (20.39-36.12)	6.01 (2.08)	0.5	41.16 (26.98-56.74)	3.53 (0.91)	2	64.48 (42.03-84.72)	4.54 (1.36)	2.33	1.57	

Compound	MES screen				scPTZ screen				neurotoxicity screen				PI	
	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t (h)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	TD ₅₀ (mg/kg) (95% CI)	TD ₅₀ (ED ₅₀) ^{MES}	TD ₅₀ (ED ₅₀) ^{scPTZ}
<u>5l</u>	1	13.12 (8.70-20.12)	3.12 (1.03)	1	>68	--	1	62.46 (55.56-67.86)	15.48 (4.84)	4.76	--	--	--	--
<u>5n</u>	scheduled													
<u>5p</u>	scheduled													
<u>5r</u>	4	13.36 (10.393-16.258)	6.945 (2.045)	1	86.93 (71.514-108.966)	11.442 (4.493)	4	131.27 (110.848-158.464)	6.467 (1.703)	9.825	1.510	--	--	--
<u>5s</u>	4	8.87 (7.704-4.957)	13.063 (3.833)	4	>150.00	--	4	105.92 (85.053-142.591)	6.313 (1.976)	11.934	<0.706	--	--	--
<u>5t</u>	2	11.27 (8.313-12.872)	10.881 (4.272)	2	>200	--	2	124.53 (81.064-175.187)	3.924 (1.095)	11.048	<0.623	--	--	--
Phenytoin	1	6.32 (5.44-7.23)	11.24 (3.52)	1	>50	--	0.5	41.23 (36.90-46.14)	14.39 (4.82)	6.52	--	--	--	--
Carbamazepine	0.25	9.85 (8.77-10.7)	20.8 (7.15)	0.25	>50	--	0.25	47.8 (39.2-59.2)	7.98 (2.37)	4.85	--	--	--	--
Valproate	0.25	287 (237-359)	7.31 (2.48)	0.25	209 (176-249)	8.51 (2.69)	0.25	483 (412-571)	12.3 (4.01)	1.68	2.31	--	--	--

The majority of the compounds were examined for oral activity in rats. Initially doses of 50 mg/kg of the semicarbazones were administered. However as the data in Table 1 reveal, with the exception of compound 3, all compounds examined at this dose displayed activity in the MES screen. In an attempt to discern those compounds possessing marked oral activity, the dose was reduced fourfold to 12.5 mg/kg, revealing that protection in the MES screen was retained in all cases. Using the doses indicated in Table 1, neurotoxicity was absent during the 0.25-4 hour time period with the exception of compound 5l in which case 1/4 rats caused neurological deficit 1,2 and 4 hours after oral administration. Compounds 4e,5b,d,g-i,n,q,r were evaluated in the scPTZ screen at the doses indicated in Table 1 but they were either inactive (compounds 5b,d,g,i,g) or displayed only marginal activity, details of which are given below. Quantitation of selected compounds was undertaken and the figures obtained are presented in Table 3.

Table 3. Evaluation of Selected Compounds in the MES and Neurotoxicity Tests after Oral Administration to Rats

Compound	MES screen			neurotoxicity screen			PI ^a
	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t(h)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	
<u>4b</u>	2	1.59 (1.01-2.25)	3.17 (0.84)	¼-24 ^b	>500	--	>315
<u>4f</u>	2	3.43 (2.282-4.726)	4.121 (1.324)	2	>500		>145.57
<u>5c</u>	4	6.15 (3.69-9.71)	2.55 (0.69)	--	--	--	--
<u>5e</u>	2	11.44 (7.61-15.75)	4.12 (1.32)	--	--	--	--
<u>5g</u>	4	2.37 (1.54-3.62)	3.18 (0.81)	¼-24 ^b	>500	--	>210
<u>5k</u>	4	1.13 (0.713-2.005)	2.661 (0.949)		>90		>79.179
<u>5n</u>	2	5.65 (3.79-7.81)	3.65 (0.98)	¼-24 ^b	>500	--	>88
<u>5o</u>	1	3.07 (2.579-3.944)	7.114 (2.292)		>500		>162.47
<u>5p</u>	6	6.48 (2.970-15.536)	1.98 (0.753)	--	--	--	--
<u>5q</u>	2	2.63 (1.689-3.926)	3.213 (0.819)		>500		>190.02
<u>5r</u>	4	3.21 (2.252-4.636)	3.575 (1.022)		>3.22		>100.16
<u>5s</u>	4	1.68 (1.146-2.438)	4.437 (1.281)		>500		>297.24
<u>5u</u>	4	45.81 (19.481-315.522)	1.327 (0.524)				

cont'd

Compound	MES screen			neurotoxicity screen			PI ^a
	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t(h)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	
Phenytoin	2	23.2 (21.4-25.4)	15.1 (4.28)	1/4-24 ^b	>500		>21.6
Carbamazepine	1	3.57 (2.41-4.72)	3.84 (1.15)	1	361 (319-402)	11.4 (2.96)	101
Valproate	0.5	395 (332-441)	8.13 (2.76)	0.5	859 (719-1148)	6.57 (2.17)	2.17

^a PI indicates the protection index i.e. TD₅₀/ED₅₀.

^b The compound was examined 0.25, 0.5, 1, 3, 4, 6, 8, and 24 h after administration.

Further bioevaluations of compound 4b were undertaken. After intraperitoneal injection into rats, the ED₅₀ and TD₅₀ figures in the MES and neurotoxicity screens for 4b were 2.37 and 80.09 mg/kg respectively revealing a PI of 33.8. Using a kindled rat screen, the ED₅₀ figure of this compound was 3.93 mg/kg. A daily dose of 100 mg/kg of 4b was administered orally for three days to rats. Afterwards, the livers were removed and comparisons made between the hepatic tissue from treated and control animals, namely liver weights and microsomal protein yields in addition to the enzyme activities of cytochrome P450, p-nitroanisole O-demethylase, UDP-glucuronosyl transferase, sulfotransferase, ethoxyresorfin O-deethylase, pentoxyresorvfin O-dealkylase, glutathione S-transferase and quinone reductase. No differences in the properties between the livers from treated and control livers were detected ($p > 0.05$).

Both 4b and 5g were examined for proconvulsant properties in the intravenous pentylenetetrazole test in mice; the doses administered were the MES ED₅₀ and the TD₅₀ figures of 4b and 5g indicated in Table 2. Neither compound possessed this undesirable feature and using a dose of 108 mg/kg, 4b increased the time to clonus. Compounds 4b and 5g were also evaluated for their ability to prevent convulsions induced by the subcutaneous administration of bicuculline and picrotoxin in mice. The semicarbazone 4b gave partial protection in these two screens whereas 5g was inactive. In addition 4b afforded no protection in the subcutaneous strychnine test in mice.

Full details of these tests are provided below
INTRAPERITONEAL INJECTION IN MICE

In addition to the information summarized in Table 1, intraperitoneal injection of a number of compounds into mice elicited the following side effects at various

doses (mg/kg) and time intervals. First, in the scPTZ screen, myoclonic jerks were noted with the following compounds namely 4c:30,100;0.5h and 5f: 100,300;0.5h. Second continuous seizure activity was observed in the
5 scPTZ screen as follows: 4c:300;0.5h; 100,300;4h; 4d:100,300;0.5 and 4h;4i:100,300;0.5 and 4h;5i:300;0.5h; 5l:300,0.5 and 4h;5o:100,300;0.5h and 5s:300;4h. At the end of the 4 hours, continuous seizure activity followed by death resulted in the scPTZ screen when mice received
10 300 mg/kg of 5o.

ORAL ADMINISTRATION TO RATS

Using the doses indicated in Table 1, several compounds showed marginal activity in the scPTZ screen. These compounds as well as the number of rats protected
15 at different time periods are as follows: 4e:1/4 after 0.5,1,4h; 5h:1/4 after 4h; 5n:1/4 after 0.5,1,2h and 5r: 1/4 after 1,4h and 2/4 after 2 hours.

INTRAPERITONEAL INJECTION OF COMPOUND 4b IN RATS

The ED₅₀ figures, 95% CI values and slope (SE) for
20 4b in the MES screen obtained 4h after intraperitoneal injection into rats were as follows: 2.37, 1.39-3.57 and 2.65(0.76) while the corresponding TD₅₀ data were 80.09,66.14-87.27 and 17.02(6.41). The protection afforded after intraperitoneal administration of 125 and
25 250 mg/kg of 4b in the scPTZ screen was displayed in 0/2 and 1/10 rats.

KINDLED RAT TEST USING COMPOUND 4b

The kindled rat test was undertaken by reported procedures (as indicated above). Compound 4b was
30 administered orally and the animals challenged with electrical stimuli 2h later. The ED₅₀ is the dose required to reduce seizures from stage 5 to stage 3 or less and these stages are described as follows namely stage 1 is mouth and facial clonus, stage 2 is stage 1
35 plus head nodding, stage 3 is stage 2 plus forelimb clonus, stage 4 is stage 3 plus rearing and stage 5 is

stage 4 plus repeated rearing and falling. The ED_{50} (mg/kg), 95% CI and slope (SE) figures for 4b were as follows: 3.93, 2.40-6.09 and 3.62(1.10). The ED_{50} data (mg/kg, 95% CI in parentheses) and times of the test for
5 three reference drugs were as follows: phenytoin: >100, 0.25 h; carbamazepine: 28.90 (7.72-75.59), 1h and valproate: 117.41(67.98-189.02), 0.25h.

EFFECT OF CHRONIC ORAL ADMINISTRATION OF 4b ON RAT LIVERS

10 Rats were administered 100 mg/kg of 4b daily for 3 days. The livers were removed, weighed and the effect of 4b on the liver microsomal system were compared to control animals which received only the vehicle (sonicated 0.5% methylcellulose).²¹⁻²³

15 (VI) EVALUATION OF 4b AND 5g IN THE TIMED INTRAVENOUS PENTYLENETETRAZOLE TEST.

Compounds 4b and 5g in methylcellulose solution (0.5%) were injected intraperitoneally into mice. The two doses used were the approximate ED_{50} values in the
20 MES test and the TD_{50} figures. After 1h, a solution of pentylenetetrazole (0.5%), sodium chloride and sodium heparin (10 USP units/mL) in water were infused into the tail veins of mice at a rate of 0.37 mL/min (4b) and 0.34 mL/min (5g). The times from the commencement of the
25 infusion until the appearances of the first twitch and also the onset of clonus were recorded for the test and control animals. From these data, the quantities of pentylenetetrazole infused was obtained. Ten animals were used as controls and for each dose administered
30 except for the 13 mg/kg dose of 4b in which case 9 animals were employed. The figures for the times of the first twitch in seconds, quantity of pentylenetetrazole administered in mg/kg (SE) and p values were as follows:
4b(dose of 13 mg/kg): 32.2,32.3(1.4), >0.05;4b(dose of
35 108 mg/kg):32.2, 32.6(0.8), >0.05; 5g(dose of 15 mg/kg): 32.8,32.9(1.4), >0.05;5g(dose of 95 mg/kg):

34.6, 34.6(1.5), >0.05. The relevant data for the times to clonus in seconds, quantity of pentylenetetrazole administered in mg/kg (SE) and p values were as follows:
4b(dose of 13 mg/kg): 37.6, 37.6(1.5), >0.05; 4b(dose of
5 108 mg/kg): 41.5, 42.1(1.4), <0.01; 5g(15 mg/kg):
41.2, 41.2(2.6), 0.05; 5g(dose of 95 mg/kg):
44.4, 44.4(2.5), >0.05.

(VII) EVALUATION OF 4b AND 5g USING OTHER CHEMICALLY INDUCED SEIZURE MODELS.

10 Various doses of 4b and 5g were administered to mice 1h (4b) or 0.5 h (5g) before chemoconvulsant doses of bicuculline and picrotoxin were given subcutaneously to mice. Compound 4b was also examined for protective effects after subcutaneous administration of strychnine.
15 In the case of 4b, the number of animals protected in the subcutaneous bicuculline test at different doses (mg/kg) were as follows: 0/8(54), 3/8(108) and 3/8(216). In the subcutaneous picrotoxin test, the protection at various doses (mg/kg) were as follows: 1/8(27),
20 5/16(108), 2/8(216). Compound 5g showed no effect in the 12-96 mg/kg dose range in these two tests. The semicarbazone 4b afforded no protection in the subcutaneous strychnine test using a dose range of 13.5-108 mg/kg. Two animals per dose were used except in
25 the bicuculline and picrotoxin tests for 4b in which cases, 8 or 16 animals per dose were employed.

EXAMPLE 3

The compounds having the structures shown in Table 4 were prepared. The structures of the listed compounds
30 correspond to those shown in Fig. 3 identified by the same first number (12, 13, 14, 15, 16, 17 or 18), with only the substituents being identified in Table 4.

Table 4. Aryl Substituents, Physical Data and Anticonvulsant Evaluation after Intraperitoneal Injection into Mice and Oral Administration to Rats of the Compounds in Series 12-18^a

				intraperitoneal injection in mice ^b					oral administration to rats ^c						
compound	R ¹	R ²	m.p. yield (°C) %	MES screen		scPTZ		toxicity		MES screen					
				0.5h	4h	0.5h	4h	0.5h	4h	0.25h	0.5h	1h	2h	4h	
															screen
<u>12a</u>	H	F	240° 65	30	100	--	--	--	--	50	2	4	4	4	4
<u>12b</u>	H	H	224-225 60	100	300	--	--	--	--	50	--	3	4	4	4
<u>12c</u>	H	Cl	225-226 40	30	30	30	--	300	30	50	4	4	4	4	4
<u>12d</u>	H	Br	225-226 60	30	30	--	--	300	30	50	1	4	4	4	4
<u>12e</u>	H	CH ₃	219-221 50	30	100	--	--	--	--	50	3	4	4	4	4
<u>13a</u>	CH ₃	H	169-171 60	30	100	--	--	100	100	30	4	4	4	4	4
<u>13b</u>	CH ₃	F	182-184 74	30	30	100	--	300	100	12.5	--	4	4	4	4
<u>13c</u>	CH ₃	Cl	192-194 60	30	30	--	30	30	100	30	3	4	4	4	4
<u>13d</u>	CH ₃	Br	195-197 30	30	30	300	--	300	100	12.5	1	3	4	4	4

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compound	R ¹	R ²	m.p. (°C)	yield %	intraperitoneal injection in mice ^a					oral administration to rats ^b							
					MES screen		scPTZ screen	toxicity screen	MES screen								
					0.5h	4h	0.5h		4h	0.5h	4h	dose (mg/kg)	0.25h	0.5h	1h	2h	4h
					0.5h	4h	0.5h		4h	0.5h	4h	0.5h	4h	0.25h	0.5h	1h	2h
<u>13e</u>	C ₂ H ₅	H	154-156	58	30	100	--	--	100	100	30	1	4	3	3	--	
<u>13f</u>	C ₂ H ₅	F	170-172	72	30	30	100	--	300	100	12.5	--	2	4	4	4	
<u>13g</u>	C ₂ H ₅	Cl	186-188	38	30	--	300	--	300	100	30	--	1	4	4	4	
<u>13h</u>	C ₂ H ₅	Br	184-186	38	30	30	100	--	300	100	12.5	--	2	4	4	4	
<u>14a</u>	CH ₃	H	136-138	14	300	--	300	--	300	--	--	--	--	--	--	--	
<u>14b</u>	CH ₃	F	154-157	27	--	--	--	--	--	--	30	1	1	3	3	2	
<u>14c</u>	CH ₃	Cl	167-169	32	300	300	300	300	300	300	--	--	--	--	--	--	
<u>14d</u>	CH ₃	Br	183-186	28	--	--	--	--	300	--	--	--	--	--	--	--	
<u>14e</u>	C ₂ H ₅	F	156-158	55	--	--	--	--	--	300	12.5	--	--	--	--	--	
<u>14f</u>	C ₂ H ₅	Cl	136-138	15	300	300	--	--	--	--	--	--	--	--	--	--	
<u>14g</u>	C ₂ H ₅	Br	155-157	5	--	--	--	--	--	300	--	--	--	--	--	--	
<u>15a</u>	S	H	226-227	40	30	30	--	--	--	300	50	--	4	4	4	4	
<u>15b</u>	OCO	H	237-238	70	--	300	--	--	--	--	12.5	--	--	--	--	--	
<u>15c</u>	OCO	Cl	245-246	80	--	300	--	--	--	--	12.5	1	--	1	--	2	
<u>15d</u>	OCH ₃	H	212-213	52	300	300	--	100	--	--	12.5	--	--	1	1	--	

compound	R ¹	R ²	m.p. (°C)	yield %	intraperitoneal injection in mice ^a					oral administration to rats ^b						
					MES screen		scPTZ screen		toxicity screen	MES screen						
					0.5h		4h			dose (mg/kg)						
					0.5h	4h	0.5h	4h		0.5h	4h	0.25h	1h	2h	4h	
<u>15e</u>	SO ₂	H	254	40	--	300	--	--	--	--	--	--	--	--	--	--
<u>15f</u>	OSO ₂	H	146	40	30	30	30	--	300	300	12.5	1	2	2	4	3
<u>15g</u>	OSO ₂	CH ₃	205-207	70	--	---	--	--	--	--	--	--	--	--	--	--
<u>16a</u>	H	F	230-231	52	30	30	30	--	300	100	12.5	1	3	4	4	4
<u>16b</u>	H	Cl	216	40	100	30	300	--	--	100	50	1	4	4	4	4
<u>16c</u>	H	Br	212-213	30	100	30	--	300	--	300	12.5	0	1	3	4	4
<u>16d</u>	H	CH ₃	225-227	32	30	30	100	100	300	100	12.5	0	0	4	4	4
<u>16e</u>	CH ₃	H	208-210	60	100	100	300	--	--	--	30	0	4	4	4	4
<u>16f</u>	CH ₃	F	204-207	91	100	30	--	300	300	300	30	3	4	4	4	4
<u>16g</u>	C ₂ H ₅	H	131-133	16	30	30	100	100	100	100	30	--	3	4	3	4
<u>16h</u>	C ₂ H ₅	F	150-157	18	30	100	--	--	100	100	30	0	0	2	3	3
<u>17a</u>	S	O	167	56	30	30	30	30	100	30	12.5	--	2	2	3	1
<u>17b</u>	NH	O	181-183	50	300	30	30	--	100	100	12.5	--	--	--	1	2
<u>17c</u>	S	S	171-172	62	100	100	100	100	--	100	12.5	--	1	2	1	1
<u>17d</u>	NH	S	172-173	40	300	--	30	30	100	100	12.5	--	--	--	1	--

compound	R ¹	R ²	m.p. (°C)	yield %	intraperitoneal injection in mice ^a					oral administration to rats ^b						
					MES screen		scPTZ screen	toxicity screen		MES screen						
					0.5h	4h	0.5h	4h	0.5h	4h	dose (mg/kg)	0.25h	0.5h	1h	2h	4h
					0.5h	4h	0.5h	4h	0.25h	0.5h	1h	2h	4h			
<u>18a</u>	H	O	176-178	60	300	300	--	300	--	300	--	--	--	--	--	--
<u>18b</u>	CH ₃	O	160	83	30	30	100	100	100	100	12.5	1	4	2	2	1
<u>18c</u>	NHNH ₂	O	220	80	300	100	--	300	--	300	30	--	--	--	--	--
<u>18d</u>	CONH ₂	O	253	75	--	--	--	--	300	300	--	--	--	--	--	--
<u>18e</u>	H	S	146-148	80	100	100	--	300	--	300	30	1	--	--	--	1
Phenytoin			-	-	30	30	--	--	100	100	--	--	--	--	--	-
Carbamazepine			-	-	30	100	100	300	100	300	--	--	--	--	--	-
Valproate			-	-	--	--	300	--	--	--	--	--	--	--	--	-

^a Doses of 30, 100 and 300 mg/kg were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 h and 4 h after injections were made.

The lines -- indicate an absence of anticonvulsant activity and neurotoxicity.

^b The figures in the table indicate the number of rats out of 4 which were protected.

The lines -- mean that no activity was demonstrated while the designation - reveals that the compound was not screened.

These compounds were synthesized as follows, although attempts to isolate 2-phenoxypropiophenone, required in the synthesis of compound 4 ($R^1=C_2H_5$; $R^2=H$), were unsuccessful; the reactions invariably leading to the formation of a number of compounds. The intermediate aldehydes and ketones were reacted with semicarbazide (13-16), thiosemicarbazide (17a,c), aminoguanidine (17b,d), formic acid hydrazide (18a,e), acetic hydrazide (18b), carbohydrazide (18c) or oxamic hydrazide (18d).

Initial anticonvulsant evaluation of compounds 13-18 was undertaken as follows. Doses of 30, 100 and 300 mg/kg were injected by the intraperitoneal route into mice and evaluated in the MES, scPTZ and neurotoxicity screens one half and four hours after administration. The results are presented in Table 4 above in addition to the data for 12a-e which is included for comparative purposes.

Quantitation of the activity of selected compounds was undertaken and these results are indicated in Table 5.

Table 5. Quantitation of the Activity of Certain Compounds in the MES, scPTZ and Neurotoxicity Screens after Intraperitoneal Injection in Mice

Compound	MES screen			scPTZ screen			neurotoxicity screen			PI ^a
	t	ED ₅₀ (mg/kg)	slope	t	ED ₅₀ (mg/kg)	slope	t	TD ₅₀ (mg/kg)	slope	
	(h)	(95% CI)	(SE)	(h)	(95% CI)	(SE)	(h)	(95% CI)	(SE)	scPTZ
<u>12a</u>	1	12.86 (10.54-17.09)	8.28 (3.00)	1	>54	-	1	108.03 (71.52-157.52)	3.69 (0.96)	-
<u>13a</u>	0.25	9.08 (6.45-11.31)	6.21 (1.91)	0.25	43.31 (18.36-112.07)	1.54 (0.57)	1	73.48 (64.32-86.40)	10.51 (3.08)	1.70
<u>13b</u>	1	11.63 (10.96-12.48)	22.69 (9.34)	0.25	>80	-	2	60.74 (58.92-63.84)	45.21 (14.45)	-
<u>13f</u>	1	5.46 (4.57-6.46)	11.64 (3.74)	2	12.84 (8.25-18.55)	3.34 (1.16)	2	35.26 (25.02-43.44)	6.78 (2.05)	2.75
<u>13g</u>	4	11.09 (10.367-12.583)	20.278 (6.827)					<100	<9.017	
<u>15a</u>	1	15.62 (10.45-20.56)	4.50 (1.36)	1	>46	-	2	181.00 (122.53-250.73)	4.59 (1.27)	-
<u>15f</u>	0.5	25.27 (21.50-29.87)	9.52 (3.00)	0.5	>100	-	1	113.00 (103.02-122.68)	17.38 (5.73)	-

MES screen			scPTZ screen			neurotoxicity screen			PI ^a		
Compound	t	ED ₅₀ (mg/kg)	slope	t	ED ₅₀ (mg/kg)	slope	t	TD ₅₀ (mg/kg)	slope	MES	scPTZ
(h)		(95% CI)	(SE)	(h)	(95% CI)	(SE)	(h)	(95% CI)	(SE)		
<u>16a</u>	1	12.37 (9.247-16.128)	6.372 (1.915)	1	>120	-	2	88.00 (83.311-94.847)	24.001 (6.853)	7.112	<0.733
<u>16b</u>	1	16.22 (14.63-17.59)	23.21 (8.59)	1	>120	-	2	53.18 (41.42-72.54)	5.90 (1.89)	3.28	-
<u>16c</u>	2	24.37 (18.45-30.93)	5.92 (1.72)	2	>200	-	2	122.57 (101.63-149.51)	6.92 (2.10)	5.03	-
<u>16d</u>	1	9.46 (6.353-13.026)	3.676 (0.986)	1	>300	-	4	196.52 (174.429-226.477)	12.821 (3.957)	20.776	<0.655
Phenytoin	2	6.48 (5.66-7.24)	12.4 (3.60)	2	>50	-	0.5	42.8 (36.4-47.5)	10.2 (3.13)	6.60	-
Carbam- azepine	0.25	9.85 (8.77-10.7)	20.8 (7.15)	0.25	>50	-	0.25	47.8 (39.2-59.2)	7.98 (2.37)	4.85	-
Valproate	0.25	287 (237-359)	7.31 (2.48)	0.25	209 (176-249)	8.51 (2.69)	0.25	483 (412-571)	12.3 (4.01)	1.68	2.31

^a The protection index (PI) is obtained by dividing the TD₅₀ figures by the ED₅₀ values.

Evaluation of most of the semicarbazones and analogs in the MES and neurotoxicity tests after oral administration to rats was performed. At the doses indicated in Table 4, neurotoxicity was absent and some
5 of the compounds examined in the scPTZ screen were either inactive or afforded only minimal protection. Hence only the MES data are presented in Table 4. The ED₅₀ figures of several compounds in the rat oral MES screen are given in Table 6.

Table 6. Quantitation of the Activity of Selected Compounds in the MES and Neurotoxicity Screens after Oral Administration to Rats

Compound	MES screen			Neurotoxicity screen			PI ^a
	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t(h)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	
<u>12a</u> ^b	2	1.59 (1.01-2.25)	3.17 (0.84)	¼-24 ^c	>500 -	- -	>315
<u>13a</u>	4	9.73 (6.440-14.141)	3.844 (1.300)	-	-	-	-
<u>13b</u>	2	3.37 (2.37-4.72)	5.74 (1.80)	2	108.77 (80.26-177.74)	4.82 (1.82)	32.3
<u>13c</u>	4	2.92 (2.203-3.464)	5.774 (1.595)	4	<500	-	<170.73
<u>13d</u>	4	1.52 (0.989-2.300)	3.600 (1.024)	-	>500	-	>328.28
<u>13e</u>	0.5	23.08 (14.33-36.64)	3.14 (0.92)	-	- -	- -	-
<u>13f</u>	2	4.25 (2.89-5.97)	3.67 (1.04)	4	>72(<240) -	>16.9(<56.436) -	
<u>13g</u>	2	2.89 (1.568-5.294)	2.035 (0.594)	0	>500	-	>172.81
<u>13h</u>	4	4.39 (2.67-5.833)	4.206 (1.279)				
<u>14b</u>	2	43.37 (25.078-66.343)	2.287 (0.569)				
<u>15a</u>	4	4.29 (3.20-5.24)	6.02 (2.00)	¼-24	>496 -	- -	>115.6

Compound	MES screen			Neurotoxicity screen			PI ^a
	t (h)	ED ₅₀ (mg/kg) (95% CI)	slope (SE)	t(h)	TD ₅₀ (mg/kg) (95% CI)	slope (SE)	
<u>16a</u>	2	4.98 (3.24-7.01)	3.92 (1.10)	4	183.05 (100.59-338.35)	2.49 (0.86)	36.8
<u>16f</u>	2	9.11 (6.185-11.658)	5.285 (1.496)	-	-	-	-
<u>16g</u>	2	18.58 (14.195-25.038)	5.238 (1.674)	-	-	-	-
<u>18b</u>	0.5	18.66 (12.40-27.60)	3.93 (1.11)	2	>125 -	- -	>6.70
Phenytoin	2	23.2 (21.4-25.4)	15.1 (4.28)	¼-24 ^c	>500 -	- -	>21.6
Carbamazepine	1	3.57 (2.41-4.72)	3.84 (1.15)	1	361 (319-402)	11.4 (2.96)	101
Valproate	0.5	395 (332-441)	8.13 (2.76)	0.5	859 (719-1148)	6.57 (2.17)	2.17

^a The letters PI refer to the protection index viz TD₅₀/ED₅₀.

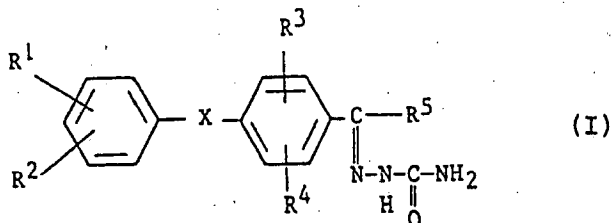
^b Data for this compound were taken from reference 1.

^c The compound was examined 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after administration.

The final pharmacological evaluation of representative compounds was undertaken using an epileptic chicken model.⁶ In this case, the convulsions which are induced by intermittent photic stimulations have been shown to be prevented by a number of anticonvulsants at blood levels similar to those used in humans. Two series of compounds were examined with the aim of observing whether oxygen or sulfur is a preferable spacer atom between the two aryl rings and also to compare the ED₅₀ figures with those obtained in the rat oral and mouse intraperitoneal screens. The ED₅₀ values of the ethers 12a-d were 1.5, 2.5, 1.0 and 2.0 mg/kg respectively and for the thioethers bearing the same aryl substitution pattern namely 16a, 15a, 16b, c, the figures were 1.5, 2.5, 1.0 and 1.5 mg/kg respectively. Hence potencies are unaffected by whether oxygen or sulfur are used as the spacer group. The ED₅₀ values of 12a, 15a, 16a in the rat oral screen are in the 1-5 mg/kg range whereas for 12a, 15a, 16b, c the figures in the mouse intraperitoneal test are approximately 15-25 mg/kg. Hence the results from the epileptic chicken model are comparable with the data provided in the rat oral screen.

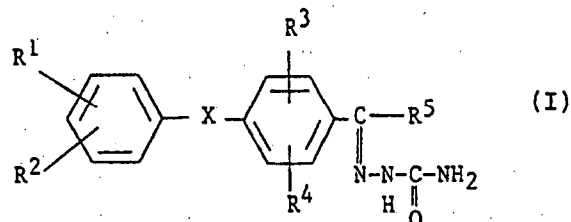
Claims:

1. A compound characterized by general formula I:



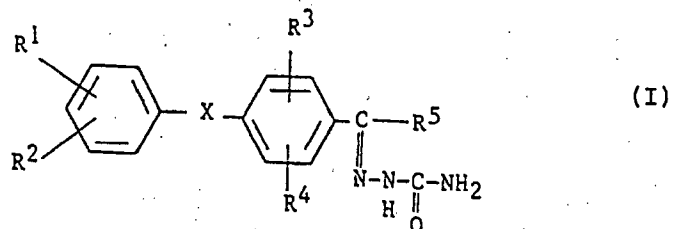
- wherein: R^1 , R^2 , R^3 and R^4 may be the same or different and each represents a hydrogen or halogen atom, or a C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy or C_{6-10} aryloxy group; R^5 represents a hydrogen atom or a C_{1-9} alkyl, C_{3-9} cycloalkyl or C_{6-10} aryl group; and X is oxygen or sulfur; except that R^1 , R^2 , R^3 , R^4 and R^5 may not all be hydrogen; or a pharmaceutically-acceptable salt thereof.
2. A compound according to claim 1 characterized in that R^1 and R^2 may be the same or different and each represents hydrogen or halide, R^3 and R^4 are each hydrogen, R^5 is hydrogen or C_{1-3} alkyl, and X is O or S.
3. A compound according to claim 1 characterized in that R^1 and R^2 represent hydrogen or fluorine, R^5 is hydrogen and X represents oxygen.
4. 4-(4'-Fluorophenoxy)benzaldehyde semicarbazone or a pharmaceutically-acceptable salt thereof.
5. 4-(Thiophenoxy)benzaldehyde semicarbazone or a pharmaceutically-acceptable salt thereof.

6. A composition for treatment of diseases of the central nervous system, characterized in that said composition contains a compound of general formula I:



- 5 wherein: R^1 , R^2 , R^3 and R^4 may be the same or different and each represents a hydrogen or halogen atom, or a C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy or C_{6-10} aryloxy group; R^5 represents a hydrogen atom or a C_{1-9} alkyl, C_{3-9} cycloalkyl or C_{6-10} aryl group; and X is oxygen or
- 10 sulfur; or a pharma-ceutically-acceptable salt thereof; and a pharmaceutically-acceptable excipient.
7. A composition according to claim 6 characterized in that R^1 and R^2 may be the same or different and each represents hydrogen or halide, R^3 and R^4 are each
- 15 hydrogen, R^5 is hydrogen or C_{1-9} alkyl, and X is O or S.
8. A composition according to claim 6 characterized in that R^1 and R^2 represent hydrogen or fluorine, R^5 is hydrogen and X represents oxygen.
9. A composition according to claim 6 characterized in
- 20 that said compound is 4-(4'-fluorophenoxy)benzaldehyde semicarbazone or a pharmaceutically-acceptable salt thereof.
10. A composition according to claim 6 characterized in that said compound is 4-(thiophenoxy)benzaldehyde
- 25 semicarbazone or a pharmaceutically acceptable salt thereof.

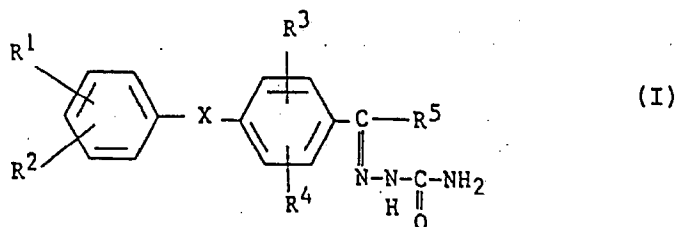
11. A method of preparing a compound of general formula I:



wherein: R^1 , R^2 , R^3 and R^4 may be the same or different
 5 and each represents a hydrogen or halogen atom, or a C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy or C_{6-10} aryloxy group; R^5 represents a hydrogen atom or a C_{1-9} alkyl, C_{3-9} cycloalkyl or C_{6-10} aryl group; and X is oxygen or sulfur; except that R^1 , R^2 , R^3 , R^4 and R^5 may not all be
 10 hydrogen;

which method is characterized by forming an intermediate aryloxy- or arylthio-arylaldehydes or ketones by reacting a corresponding (thio)phenol with fluorobenzaldehyde or a fluoroaryl ketone in a solvent
 15 in the presence of potassium carbonate at temperatures in the range of 100 to 200°C under a non-oxidizing gas, extracting the intermediate and then reacting the intermediate with semicarbazide and collecting the resulting precipitate of the desired compound.

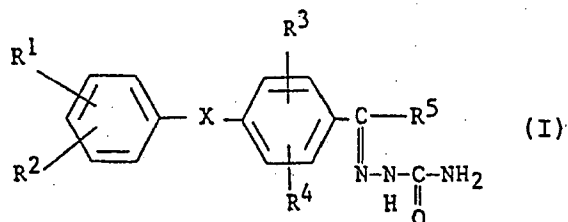
20 12. A method of preparing a compound of general formula I:



wherein: R^1 , R^2 , R^3 and R^4 may be the same or different and each represents a hydrogen or halogen atom, or a C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy or C_{6-10} aryloxy group; R^5 represents a hydrogen atom or a C_{1-9} alkyl, C_{3-9} cycloalkyl or C_{6-10} aryl group; and X is oxygen or sulfur; except that R^1 , R^2 , R^3 , R^4 and R^5 may not all be hydrogen;

which method is characterized in that intermediate aldehydes were prepared by adding benzoyl chloride or 4-chlorobenzoyl chloride to a solution of 4-hydroxybenzaldehyde in pyridine, pouring the reaction mixture onto acetic acid, collecting the precipitate and recrystallizing said precipitate to give 4-benzoyloxybenzaldehyde or 4-(4-chlorobenzoyloxy)benzaldehyde.

13. A method of treating a human or animal patient for a disorder of the central nervous system, characterized by administering to said patient an effective amount of a compound having the general formula I:



wherein: R^1 , R^2 , R^3 and R^4 may be the same or different and each represents a hydrogen or halogen atom, or a C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy or C_{6-10} aryloxy group; R^5 represents a hydrogen atom or a C_{1-9} alkyl, C_{3-9} cycloalkyl or C_{6-10} aryl group; and X is oxygen or sulfur; or a pharmaceutically-acceptable salt thereof.

14. A method according to claim 12 characterized in that said disorder exhibits convulsions or seizures.

15. A method according to claim 12 characterized in that said disorder is a exhibits epileptic seizures.

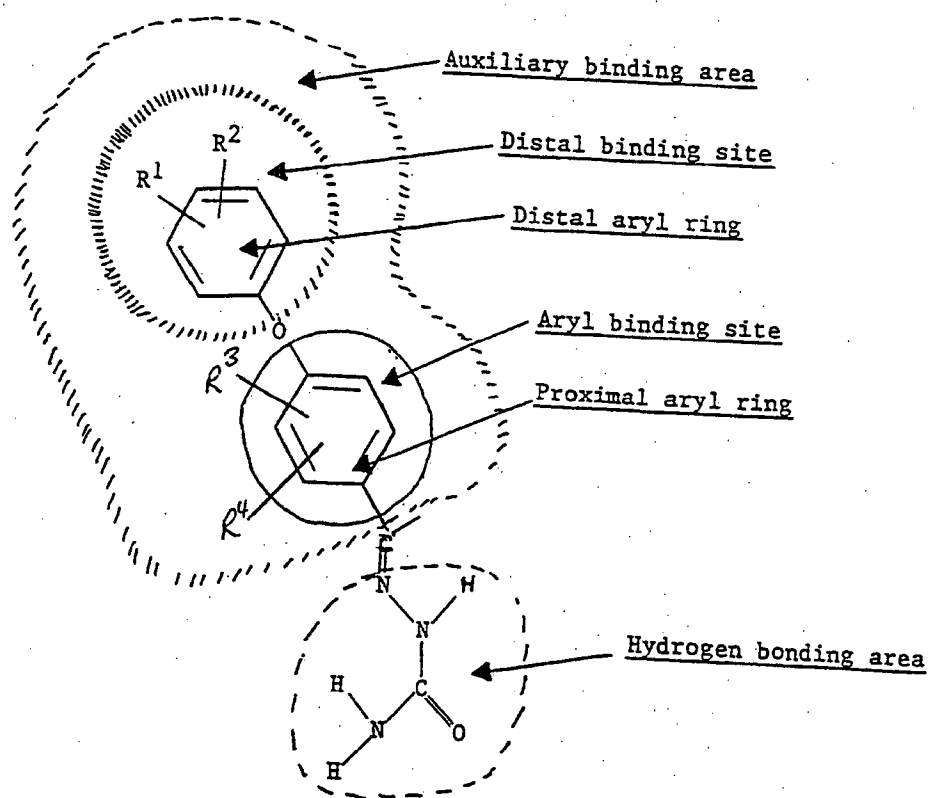


Fig. 1

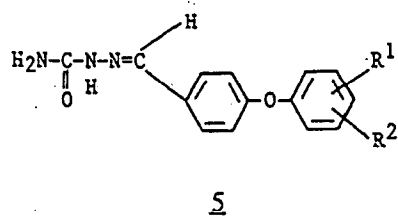
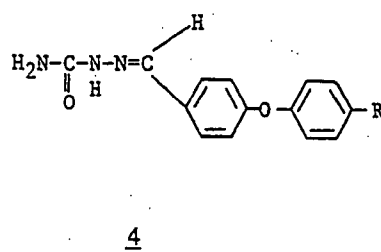
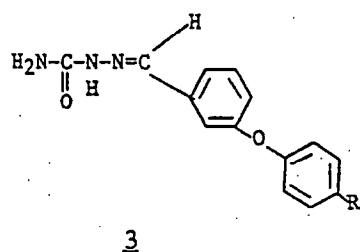
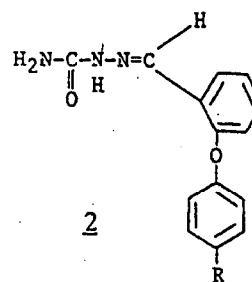


Fig. 2

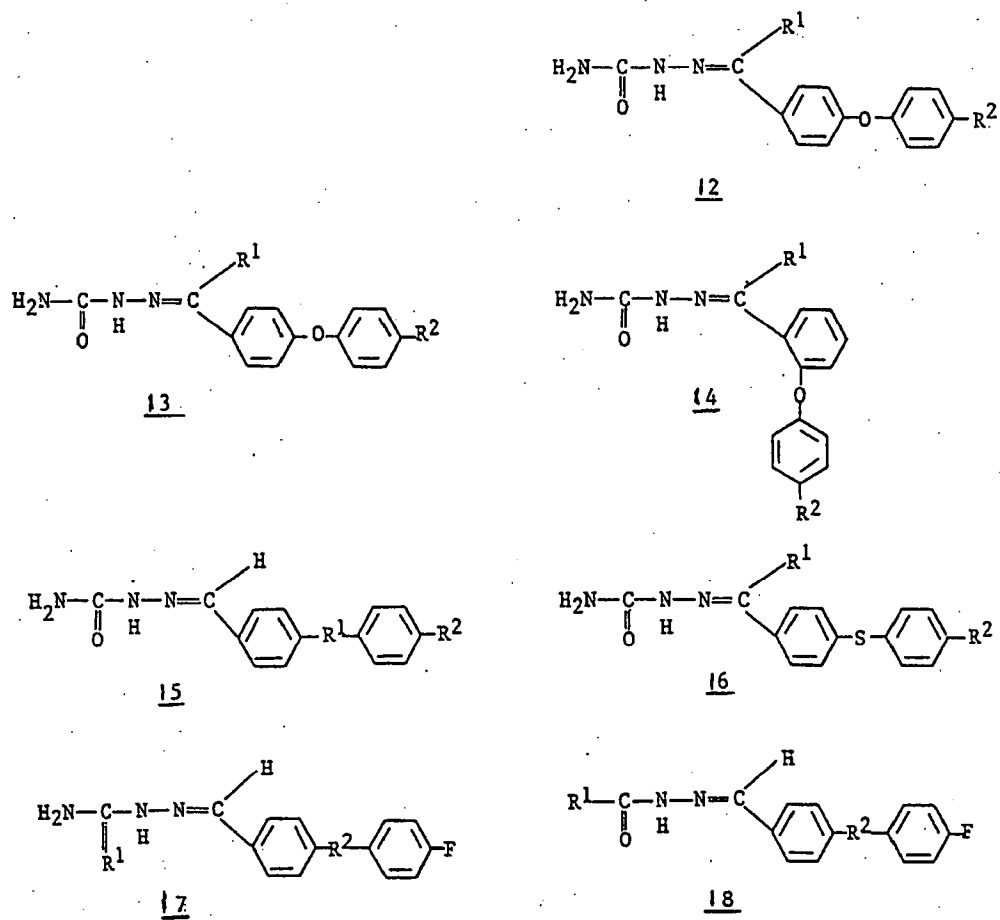


Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 96/00380

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07C281/14 A61K31/175

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014745 see BRN 2542223 & J. ORG. CHEM., vol. 26, 1961, pages 2353-55, ---	1
X	DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014746 see BRN 1890700, 3400167, 3400193, 3410343, 3419487, 3421220, 3436628 & BULL. SOC. CHIM. FR., 1954, page 644,646 --- -/--	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

1 October 1996

Date of mailing of the international search report

10. 10. 96

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INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/CA 96/00380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014747 see BRN 3396690 & YAKUGAKU ZASSHI, vol. 72, 1952, page 300</p> <p>---</p>	1
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014748 see BRN 3389800 & J. CHEM. SOC., 1942, page 347, 353</p> <p>---</p>	1
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014749 see BRN 3417848 & J. AMER. CHEM. SOC., vol. 65, 1943, page 1736, 1738</p> <p>---</p>	1
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014750 see BRN 3422330, 3449771 & YAKUGAKU ZASSHI, vol. 73, 1953, page 243</p> <p>---</p>	1
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014751 see BRN 3382967 & J. AMER. CHEM. SOC., vol. 58, 1936, page 1808, 1810</p> <p>---</p>	1
X	<p>DATABASE CROSSFIRE Beilstein Informationsgesellschaft GmbH XP002014752 see BRN 3347507 & YAKUGAKU ZASSHI, vol. 57, 1937, page 36, 37</p> <p>---</p>	1,5
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Internal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRYCHIMICA THERAPEUTICA., vol. 26, no. 5, 1991, PARIS FR, pages 529-34, XP002014742 J. R. DIMMOCK ET AL.: "Evaluation of the thiosemicarbazones of some aryl alkyl ketones and related compounds for anticonvulsant activities" cited in the application see whole document; especially scheme 1, compound 1n; page 531, table 1; ---</p>	1,6,13
A	<p>PHARMAZIE, vol. 46, no. 7, 1991, BERLIN DE, pages 538-539, XP002014743 J. R. DIMMOCK ET AL.: "Evaluation of some mannich bases of 1-aryl-1-ethanones and related ketones for anticonvulsant activities" see page 539, compound 2f ---</p>	1,6,13
A	<p>EUR. J. MED. CHEM. (1995), 30(4), 287-301, XP002014744 DIMMOCK, J. R. ET AL: "Some aryl semicarbazones possessing anticonvulsant activities" see the whole document ---</p>	1,6,13
A	<p>WO,A,94 06758 (UNIV SASKATCHEWAN) 31 March 1994 see the whole document ---</p>	1,6,13
A	<p>SYNTHESIS, no. 1, 1991, STUTTGART DE, pages 63-8, XP002014786 G. W. YEAGER ET AL.: "A convenient method for the preparation of 4-aryloxyphenols" cited in the application see page 65, right-hand column, line 8 - line 24 ---</p>	11
A	<p>EP,A,0 065 485 (CIBA GEIGY AG) 24 November 1982 see page 4, line 17 - line 24; claims 1,50 -----</p>	1,6,13

INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13-15 are directed to a method of treatment of the human body the search has been carried out completely and based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 96/00380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9406758	31-03-94	NONE	
EP-A-0065485	24-11-82	AU-B- 562239	04-06-87
		AU-A- 8358482	18-11-82
		BG-B- 60715	31-01-96
		CA-A- 1192203	20-08-85
		GB-A,B 2098607	24-11-82
		MD-B- 5	31-03-94
		OA-A- 7097	31-01-87
		SU-A- 1178309	07-09-85
		SU-A- 1436855	07-11-88
		US-A- 5266585	30-11-93
		JP-B- 1021147	19-04-89
		JP-C- 1536402	21-12-89
		JP-A- 58023687	12-02-83
		MD-B- 58	31-08-94
		SU-A- 1148564	30-03-85